Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. We have recently added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of both diagnostic and therapeutic progress in this area. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens.

DIAGNOSIS

PET in Plaque Imaging

Rudd et al. from the Mt. Sinai School of Medicine (New York, NY) reported in the August 28 edition of the *Journal of the American College of Cardiology* (2007;50:892–896) on a study designed to determine the near-term variability and reproducibility of ^{18}F-FDG PET imaging of atherosclerosis. The validated ability to track changes in inflammation over time would make this technique a valuable surrogate marker of antiatheroma drug efficacy. The study included 11 individuals who underwent ^{18}F-FDG PET/CT imaging of the carotid arteries and aorta at baseline and at 2 weeks. Both interobserver and intraobserver agreement on findings were quite high, and interscan plaque ^{18}F-FDG variability over 2 weeks was quite low, suggesting that spontaneous change in plaque tracer uptake over the study period was quite low. These and other data led the authors to conclude that "drug studies using ^{18}F-FDG PET imaging would require few subjects compared with other imaging modalities" and that the results of this study strengthen the case for PET as a noninvasive plaque imaging technique.

Journal of the American College of Cardiology

SPECT and LVEF in Diabetics

In an article published in the September issue of the *American Heart Journal* (2007;154:567–574), Chareonthaitawee et al. from the Mayo Clinic and Mayo Foundation (Rochester, MD) reported on a study using SPECT to determine the prevalence and prognosis of reduced left ventricular ejection fraction (LVEF) in asymptomatic diabetic patients without known coronary artery disease (CAD). The study included 1,046 such patients (69% men, 31% women) who were referred for assessment of LVEF. Each patient underwent SPECT imaging, and images were tagged low, intermediate, or high risk, based on the summed stress score. Patients were followed for a mean of 5.3 ± 3.3 years. The authors found that 175 (16.7%) study participants had moderately or severely reduced LVEF (mean LVEF of 40.0% ± 7.7%). Individuals in this group were older, had more peripheral arterial disease, and more electrocardiographic abnormalities than those without reduced LVEF. Summed stress, reversibility, and rest scores were significantly more abnormal in the reduced LVEF group. Ten-year survival was significantly lower in patients with any reduction in LVEF than in those without reduced LVEF (29% and 57%, respectively). The findings that 1 in 6 of these patients had reduced LVEF and that the annual mortality rates of the groups with and without reduced LVEF were 7% and 4%, respectively, suggested the potential benefits of routine SPECT assessment for CAD in diabetic patients.

American Heart Journal

PET Challenges After Thoracic Procedures

Festic et al. from the Mayo Clinic (Jacksonville, FL) reported in the September issue of the *Mayo Clinic Proceedings* (2007;82:1060–1064) on a study designed to investigate the hypothesis that tissue changes induced by invasive thoracic procedures may be associated with increased ^{18}F-FDG uptake on PET images and may provide special challenges to interpretation. The study included 81 patients who underwent both CT of the chest and bronchoscopy before ^{18}F-FDG PET. Of these, 45 (56%) underwent PET imaging within 4 weeks after bronchoscopy, and 13 (29%) of these 45 showed increased uptake on PET with no corresponding abnormalities on CT. In 3 (23%) these 13 patients, the authors found that positive PET findings were most likely the result of tissue changes associated with bronchoscopy. These and other findings led them to conclude that "invasive thoracic procedures may cause an increased uptake of radiotracer on PET scans that could be mistakenly interpreted as evidence of malignancy" and that "to avoid clinical misjudgment, clinicians should perform PET before invasive thoracic procedures."

Mayo Clinic Proceedings

PET/CT in Recurrent ^{131}I-Negative Thyroid Cancer

In a study e-published ahead of print on September 20 in *Annals of Surgical Oncology*, Finkelstein et al. from the Washington University School of Medicine (St. Louis, MO) reported on the utility of ^{18}F-FDG PET/CT for

detection of recurrent thyroid cancer in patients in whom whole-body ^{131}I scintigraphy (WBS) is negative. The retrospective review included the records of 65 such patients who had undergone ^{18}F-FDG PET/CT for suspected cancer recurrence, based on clinical observations or thyroglobulin levels. PET/CT abnormalities were reported in 47 patients and compared with results from surgical pathology or disease progression. Of these, 43 studies were true-positives, with 21 confirmed at surgical pathology. The 4 false-positives included an infundibular cyst, inflamed supraclavicular cyst, pneumonitis, and degenerative disc disease. Of the 18 original studies that were reported as negative, 17 were true-negatives and 1 was a false-negative (metastatic papillary carcinoma). ^{18}F-FDG PET/CT showed a patient-based sensitivity in this study of 98%, specificity of 81%, positive predictive value of 91%, and negative predictive value of 94%. The authors concluded that this technique is "useful for detecting thyroid cancer recurrence in WBS-negative patients and can assist decision making."

Annals of Surgical Oncology

CAD in Pediatric Cardiac Transplantation

Maiers and Hurwitz, from the Indiana University School of Medicine (Indianapolis) reported on September 21 ahead of print in *Pediatric Cardiology* on the use of myocardial perfusion imaging to identify and determine the incidence of transplant coronary artery vasculopathy (CAV) in pediatric patients. The study included 20 patients (11 boys, 9 girls) who underwent routine ^{99m}Tc-tetrofosmin SPECT cardiac imaging and stress echocardiography at a mean of 7.9 years (range, 1–14 years) after transplantation. Six (30%) patients had positive perfusion scans, with a mean time since transplantation of 5.6 years. Five of these patients had negative stress echocardiograms, and only 1 reported symptoms (exertional dyspnea). Neither hypertension nor rejection episodes were significantly associated with positive nuclear scans. Cardiac catheterization showed coronary disease in 2 of the 6 SPECT-positive patients and in 2 of the SPECT-negative patients. The authors emphasized that only when 3 imaging modalities (SPECT, stress echocardiography, and coronary injection) were used was the "true" incidence of CAV in this population revealed to be 30%. They concluded that pediatric coronary transplant patients "need continued evaluation by multiple modalities for detection of developing coronary lesions."

Pediatric Cardiology

PET/CT in Pediatric Sarcoma

Tateishi et al. from the National Cancer Center (Tokyo, Japan), the Tokai University School of Medicine (Kanagawa, Japan), and the University of Texas MD Anderson Cancer Center (Houston, TX) reported in the September issue of the *Journal of Pediatric Hematology/Oncology* (2007:29: 608–612) on a study designed to clarify the diagnostic utility and accuracy of ^{18}F-FDG PET/CT in the staging of pediatric sarcomas. The retrospective study included the records of 50 pediatric patients with histologically proven sarcomas who underwent PET/CT before treatment. The diagnostic accuracy of ^{18}F-FDG PET/CT in detecting nodal and distant metastases was compared with that of PET alone and conventional imaging techniques alone. The results were compared with histologic results (15 patients) and size of lesion on follow-up examinations in the remaining patients. PET/CT correctly identified nodal metastasis in 48 patients (96%), with corresponding results for PET alone and conventional imaging alone of 43 (86%) and 46 (92%) patients, respectively. PET/CT correctly identified distant metastases in 43 patients (86%), and corresponding results for PET alone or conventional imaging alone were 33 (66%) and 35 (70%) patients, respectively. PET/CT provided 7 false-negative results for distant metastasis, caused by subcentimetric lesions, bone marrow lesions, or soft tissue lesions. The authors concluded that "PET/CT is more accurate and probably more cost effective" than PET alone or conventional imaging for distant metastases in pediatric sarcomas.

Journal of Pediatric Hematology/Oncology

SPECT and Nonsymptomatic Patients with Fibrillation

In an article published in the September issue of the *Journal of the American College of Cardiology* (2007; 50:1080–1085), Askew et al. from the Mayo Clinic and Mayo Clinic College of Medicine (Rochester, MN) reported on a study designed to determine the utility of myocardial perfusion SPECT in coronary artery disease (CAD) screening of patients with atrial fibrillation (AF) but no symptoms of chest pain or dyspnea. The retrospective study included 374 such patients referred for suspicion of CAD. Each patient underwent myocardial perfusion SPECT, and the group was followed for a mean of 5.7 ± 3.8 years. The study also included a control group of 374 asymptomatic age- and gender-matched patients without AF. Overall results were quite similar in the 2 groups, including mean summed stress scores (SSS) and rates of abnormal SPECT and high-risk studies. In both groups, SSS were significant predictors of outcomes. However, both 5- and 10-year mortality rates were significantly greater in the AF group, even after adjusting for multiple clinical variables. The authors concluded that screening for CAD using stress SPECT in asymptomatic AF patients yields results similar to those in age- and gender-matched control patients, and that the increased total mortality associated with AF is independent of findings on stress SPECT. These results, they noted, "suggest that factors other than obstructive CAD are responsible for the increased mortality in AF."

Journal of the American College of Cardiology

Stereotactic PET Imaging

Novotny et al. from the University of Pittsburgh Cancer Institute (PA)

reported in the September 18 issue of *Stereotactic and Functional Neurosurgery* (2007;86:30–36) on a study evaluating 3 different techniques used for stereotactic PET image definition: PET with external stereotactic radioactive markers; PET without external stereotactic markers and subsequent coregistration with a stereotactically defined imaging modality, such as CT or MR imaging; and PET/CT imaging with utilization of external nonradioactive markers. The study was performed using a special head phantom, filled with ^{18}F-FDG in water solution at a concentration simulating counts from standard brain. A glass test vessel filled with ^{18}F-FDG/water solution at activity concentrations corresponding to pathologic lesions in PET was placed in the phantom. A Leksell stereotactic MR imaging indicator box was filled with ^{18}F-FDG/water solution at an appropriate activity concentration. The phantom was then stereotactically investigated in the treatment planning system for deviations from the center of the simulated pathological lesion using PET, PET/CT, CT, and MR imaging. The total spatial inaccuracies for stereotactic PET image definition based on radioactive fiducials for 3.4- and 2.0-mm PET slices were 1.7 and 0.7 mm, respectively. Total spatial PET image definition inaccuracy was 0.7 mm based on PET/CT imaging and stereotactic definition using nonradioactive CT fiducials. Total spatial PET image definition inaccuracy based on coregistration with MR imaging was 0.5 and with CT was 0.9 mm. The authors concluded that all 3 stereotactic PET image definition techniques evaluated in this phantom study provided entirely acceptable results for the clinical requirements of functional imaging. However, they noted that the most convenient stereotactic PET image definition technique seemed to be PET image coregistration either on CT or MR imaging, where PET imaging can be performed independently (i.e., well before) on a frame application and then coregistered with stereotactically performed CT or MR images during the stereotactic procedure. They noted that these techniques remain to be explored in patient studies.

Stereotactic and Functional Neurosurgery

PET and Huntington's Onset

In an article e-published on September 24 ahead of print in *Brain*, Feigin and a group of researchers from North Shore–Long Island Jewish Health System (Manhasset, NY), New York University School of Medicine (New York, NY), the Transitional Learning Centre (Galveston, TX), the University of Toronto (Canada), and the University of Iowa (Des Moines) reported on the use of ^{11}C and ^{18}F-FDG PET in assessing metabolic changes in asymptomatic individuals who carry the Huntington's disease (HD) gene. The study included 12 such participants who were imaged at baseline and at 18 and 44 months. The authors found that striatal D_2 binding declined over time and that the activity of a reproducible HD-related metabolic covariance pattern increased between baseline and 18 months but declined at 44 months. These network changes also coincided with progressive declines in striatal and thalamic metabolic activity. Striatal metabolism was abnormally low at all time points, and thalamic metabolism was elevated at baseline but fell to subnormal levels in participants who developed symptoms. The authors concluded that "increases in network expression and thalamic glucose metabolism may be compensatory for early neuronal losses" in asymptomatic individuals who carry the HD gene and that "declines in these measures may herald the onset of symptoms."

Brain

PET Uptake as Predictive Biomarker in Cervical Cancer

Kidd et al. from the Washington University School of Medicine (St. Louis, MO) reported on September 4 ahead of print in *Cancer* on a study evaluating the ability of cervical tumor uptake (maximized standard uptake value [SUV_{max}]) of ^{18}F-FDG as evaluated by PET to serve as a biomarker of response and prognosis in patients with cervical cancer. The study population included 287 patients with stage IA2 through IVB cervical cancer who underwent PET imaging before proceeding to surgery, chemoradiation, or palliation. The mean SUV_{max} was 11.4, with a wide range of 1–50.4. Mean tumor volumes were 42.1 cm^3 for stage I, 63.7 cm^3 for stage II, 129.2 cm^3 for stage III, and 166.2 cm^3 for stage IV tumors. No correlation was found between tumor volume and SUV_{max} or between type of tumor histology and SUV_{max}. Higher SUV_{max} was associated with an increased risk of lymph node metastasis at diagnosis. The researchers analyzed the relationships of tumor histology, lymph node metastasis, tumor volume, and SUV_{max} to subsequent death from cervical cancer over all participants in the study and found SUV_{max} to be the only significant independent predictive factor. Participants with an $SUV_{max} \leq 5.2$ had a 95% 5-year survival rate; for those with an $SUV_{max} > 5.2$ and ≤ 13.3, this rate was 70%; and for those with an $SUV_{max} > 13.3$, this rate was 44%. Increased SUV_{max} was also associated with persistent abnormal uptake in the cervix at 3-month PET evaluation in the 238 patients who received curative chemoradiation therapy. The authors concluded that "the SUV_{max} of the cervical tumor at diagnosis was a sensitive biomarker of treatment response and prognosis for patients with cervical cancer."

Cancer

THERAPY

Phase 1 NHL RIT in Children

Cooney-Qualter et al. from Columbia University (New York, NY) reported in the September 15 issue of *Clinical Cancer Research* (2007;13:5652S–5660) on initial studies to answer questions about the safety and feasibility of ^{90}Y-ibritumomab tiuxetan

radioimmunotherapy (RIT) in children or adolescents with relapsed or refractory CD20+ non-Hodgkin's lymphoma. Five such participants were included in this phase I RIT study. Each received rituximab on days 0 and 7 and ^{111}In-ibritumomab tiuxetan on day 0. Immediately after rituximab on day 7, patients received ^{90}Y-ibritumomab tiuxetan if dosimetry study results fulfilled criteria of <2000 cGy exposure to all solid organs, <300 cGy to marrow, and 0.4 mCi/kg in patients with good marrow reserve (n = 3) and 0.1 mCi/kg in patients with poor marrow reserve after bone marrow transplant (n = 2). Except for 1 incident of rituximab infusion–related chills, no toxicities nor incidences of human antimurine/antichimeric antibodies were noted. Based on their results, the authors have begun an expanded, limited-institutional phase II study to further evaluate the safety, tolerability, and response rate with ^{90}Y-ibritumomab tiuxetan dose stratification based on marrow reserve. They noted that this approach appears promising in this patient group for which current therapeutic choices are limited.

Clinical Cancer Research

RIT of Fungal Infection

Also in the September 15 issue of *Clinical Cancer Research* (2007;13: 5629S–5635S), Dadachova et al. from the Albert Einstein College of Medicine (Bronx, NY) reported on in vitro and in vivo studies designed to identify the best delivery vehicle for organism-specific monoclonal antibodies in radioimmunotherapy (RIT) of human pathogenic fungal infections. The group has previously performed comparative evaluation of capsular polysaccharide-specific antibodies with IgG1 and IgM isotypes and F(ab′)(2) and Fab fragments to identify Cryptococcus neoformans (CN). In this study, 18B7 IgG1 and 13F1 IgM and their isotype-matching controls were radiolabeled with ^{188}Re, and their binding to 2 CN strains was evaluated in vitro using a cellular dosimetry algorithm. Biodistribution studies of ^{188}Re-labeled 18B7 and 13F1 and ^{111}In-labeled 18B7 and its F(ab′)(2) and Fab fragments were performed in A/JCr mice systemically infected with a CN strain. In the in vitro studies, 18B7 IgG1 was found to be superior to 13F1 IgM binding. Substantial killing of 24067 and H99 CN cells was achieved with 1 μCi ^{188}Re-18B7, with no killing observed for 1 μCi ^{188}Re-13F1. In in vivo studies, ^{188}Re-18B7 localized specifically in the lungs of CN-infected mice, but uptake of ^{188}Re-13F1 was nonspecific. ^{111}In-F(ab′)(2) fragments showed higher uptake in the lungs and lower uptake in the liver than intact ^{111}In-18B7 at 48 hours. The authors concluded that "comparative evaluation of IgG and IgM and of F(ab′)(2) and Fab fragments as potential delivery vehicles for RIT of cryptococcal infection strongly suggests that affinity for the target antigen is an important prerequisite for successful targeting of infection in vivo and that in vitro affinity measurements may predict the in vivo efficacy of candidate monoclonal antibodies."

Clinical Cancer Research

MOLECULAR IMAGING

Molecular Mimics and RIT

Balhorn et al. from the Lawrence Livermore National Laboratory (CA) and the University of California, Davis (Sacaramento) reported in the same issue of *Clinical Cancer Research* (2007; 15:5621S–5628S) on a new approach for radioimmunotherapeutic (RIT) delivery of radionuclides in non-Hodgkin's lymphoma (NHL) and leukemia using small synthetic molecules that mimic the targeting properties of the Lym-1 antibody that binds selectively to HLA-DR10 on malignant B-cell lymphocytes. The researchers used advanced computational methods to predict 2 sets of small molecules that would bind to neighboring cavities on the β subunit of HLA-DR10 surrounding a critical amino acid in the Lym-1 epitope, and nuclear MR spectroscopy confirmed ligand binding to the cell surface protein. Pairs of these molecules were then chemically linked together to produce a series of synthetic high-affinity ligands (SHALs) that bind only to cell lines expressing HLA-DR10. Additional analyses of biopsy sections obtained from patients confirmed that SHALs bound to both small and large cell NHLs, mimicking the selectivity of Lym-1. The authors concluded that their results showed "that synthetic molecules less than 1/50th the mass of an antibody can be designed to exhibit strong binding to subtle structural features on cell surface proteins similar to those recognized by antibodies" and that "this approach offers great potential for developing small molecule therapeutics that target other types of cancer and disease."

Clinical Cancer Research

PET and Bioluminescence of siRNA Nanoparticles

In a study e-published on September 17 ahead of print in the *Proceedings of the National Academy of Sciences*, Bartlett et al. from the California Institute of Technology (Pasadena) reported on the use of PET and bioluminescent imaging for in vivo quantification of the effects of tumor-specific targeting on the biodistribution and efficacy of small interfering RNA (siRNA) nanoparticles. The researchers conjugated 1,4,7,10-tetraazacyclododecane-1,4,7, 10-tetraacetic acid to the 5′ end of the siRNA molecules, facilitating ^{64}Cu labeling for PET. Mice bearing luciferase-expressing Neuro2A subcutaneous tumors underwent bioluminescent imaging before and after PET imaging to allow correlation of functional efficacy with biodistribution data. Both nontargeted and transferrin-targeted siRNA nanoparticles showed similar biodistribution and tumor localization with PET, but, at 1 day after injection, transferrin-targeted siRNA nanoparticles reduced tumor luciferase activity by approximately 50% compared with nontargeted nanoparticles. The authors noted that because the primary advantage of targeted nanoparticles is associated with processes involved in cellular uptake in tumor cells rather than overall tumor localization, optimization of

internalization through techniques such as this may be key for the development of effective nanoparticle-based targeted therapeutics.

Proceedings of the National Academy of Sciences

Molecular Analysis of Thyroid Cancer Without ^{131}I Uptake

Mian et al. from the University of Padua (Italy) reported on September 14 ahead of print in *Clinical Endocrinology (Oxford)* on a histologic study of the molecular characteristics associated with a subset of papillary thyroid cancers (PTCs) with no ^{131}I uptake. The study included 48 PTC tissues divided into 3 groups: (1) 28 primary cancers; (2) 7 recurrences capable of trapping ^{131}I; and (3) 13 recurrences incapable of trapping ^{131}I. mRNA levels of sodium/iodide symporter (NIS), thyroglobulin, and thyroperoxidase and pendrin genes, glycolytic metabolism genes, and BRAF mutations were assessed and compared among the groups. Tissues with no ^{131}I uptake had slightly reduced NIS; significantly reduced thyroglobulin, thyroperoxidase, and pendrin; and significantly increased GLUT-1 gene expression levels and a high frequency of BRAF mutations (77%). A BRAF (V600E) mutation in both primary and metastatic thyroid cancers was associated with a marked drop in thyroperoxidase and pendrin expression and a considerable increase in GLUT-1 expression. The authors concluded that the loss of ^{131}I uptake in recurrences depends not only on a decrease in NIS gene activity but possibly on a reduction in the molecules regulating its intracellular metabolism, that the high GLUT-1 gene expression supports the use of PET with specific tracers in the clinical management of such cancers, and that BRAF (V600E) point mutations may lead to less differentiated phenotypes, suggesting worse prognoses.

Clinical Endocrinology (Oxford)

MR Microparticle Imaging of Acute Brain Inflammation

McAteer et al. from the University of Oxford (UK) reported on September 23 ahead of print in *Nature Medicine* on in vivo MR imaging of acute brain inflammation using iron oxide microparticles, a technique with specific promise in monitoring the expression of endovascular molecules in early identification and treatment of multiple sclerosis and other diseases. The authors described in vivo MR detection of endothelial vascular cell adhesion molecule-1 in acute brain inflammation in a mouse model when other pathology, symptoms, and means of detection were negative. Their use of antibody-conjugated microparticles carrying large amounts of iron oxide provided "potent, quantifiable contrast effects that delineate the architecture of activated cerebral blood vessels" and offered rapid clearance from blood results with minimal background contrast.

Nature Medicine

Refining Stem Cells in Ischemic Injury

Li et al. from Stanford University (CA) reported in a September 11 supplement to *Circulation* (2007;116[11 suppl]:I46–I54) on a study that characterized the differentiation of embryonic stem cell–derived endothelial cells (ESC-ECs), applied molecular imaging techniques to examine their survival in vivo, and investigated the therapeutic efficacy of ESC-ECs for restoration of cardiac function after ischemic injury. The authors isolated murine ESC-ECs that expressed endothelial cell markers similar to adult mouse lung endothelial cells, formed vascular-like channels, and incorporated fluorescence dye DiI-labeled acetylated low-density lipoprotein. ES cells were transduced with a ubiquitin promoter driving firefly luciferase and monomeric red fluorescence protein. ESC-ECs or phosphate buffered saline (PBS) were injected into the hearts of mice undergoing left anterior descending artery ligation. Bioluminescence imaging indicated survival of transplanted ESC-ECs for approximately 8 weeks, and echocardiography indicated significant functional improvement in the ESC-EC group compared with controls. Postmortem analysis confirmed increased small capillaries and venules in infarcted zones in the EC group. The authors concluded that "with further validation, these ESC-ECs could become a valuable source of cell therapy for induction of angiogenesis in the treatment of myocardial ischemia."

Circulation

High-Resolution Photoacoustic Tomography

Yang et al. from South China Normal University (Guangzhou, China) reported in the August issue of *Medical Physics* (2007;34:3294–3301) on functional imaging of cerebrovascular activity in small animals using high-resolution photoacoustic tomography. Photoacoustic imaging (PAI) is a noninvasive, nonionizing modality based on data derived from differences in light absorption of biological tissues. The authors noted that PAI offers "the endogenous contrast characteristics of traditional optical imaging, while benefiting from high spatial resolution of the ultrasound imaging." They developed a PAI system to reconstruct a 2D cross-sectional image and visualize the cerebrovascular activities of mouse in vivo, producing a spatial resolution of 0.110 mm. They demonstrated several potential applications of the technique by successfully mapping a traumatic lesion in the mouse brain cerebral cortex, by monitoring physiological changes in the brain resulting from carotid ligation and drug stimulation, and providing 2D sliced images of a mouse brain injury at different depths. They concluded that these experimental results indicate that PAI has excellent potential for assessing traumatic brain injury and physiologic function in the brain.

Medical Physics